

Synthesis of Brevicomins, Principal Sex Attractant of Western Pine Beetle

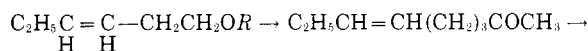
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A practical method for the large-scale preparation of *exo*-7-ethyl-5-methyl-6,8-dioxabicyclo(3.2.1)octane (brevicomins) is described. A key reaction was the stereoselective ring closure of the oxido ketone formed in situ from epoxidation of *cis*-6-nonen-2-one.

The sex attractant of the western pine beetle, *Dendroctonus brevicomis*, was shown (2) to be a three-component mixture of myrcene, frontalin [1,5-dimethyl-6,8-dioxabicyclo(3.2.1)octane], and *exo*-brevicomins [*exo*-7-ethyl-5-methyl-6,8-dioxabicyclo(3.2.1)octane]. Two prior syntheses of the main factor, brevicomins, have appeared (1, 3); however, these were impractical for the large quantities required for field testing. A simple process partially based on the method of Wasserman and Barber (3) has been developed.

cis-3-Hexene-1-ol (I) was converted to its tosylate ester (II) in 86% yield, which in turn was used to alkylate ethyl acetoacetate. The crude keto ester intermediate was carefully hydrolyzed by stirring with aqueous 1*N* sodium hydroxide at ambient temperature for 48 hr. The resultant solution was acidified and boiled to cause decarboxylation to afford *cis*-6-nonen-2-one (III) in 37% yield from II. The application of heat or significant amounts of alcoholic cosolvent in the alkaline hydrolysis medium promoted Claisen cleavage of the keto ester intermediate with drastic lowering of the yield of ketone III.

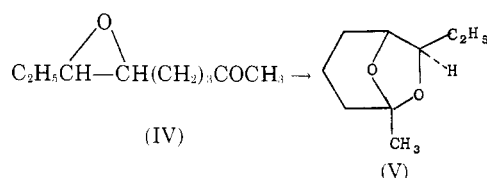
cis-6,7-Oxidononan-2-one (IV) could be obtained by treatment of III with *m*-chloroperbenzoic acid, but thermal rearrangement (2) gave low yields of *exo*-brevicomins (V) along with polymeric material. It was found that if the epoxidation was conducted in benzene below 15°C followed by subsequent refluxing of the solution, a 55% yield of 95% *exo*-5% *endo*-brevicomins was obtained. Since the starting hexenol (I) contained only 5% *trans* isomer, a stereoselective ring opening has taken place. Protonation of the oxide by chlorobenzoic acid along with concerted attack by the ketonic oxygen would account for this selectivity.



(I) R = H

(II) R = Tosyl

(III)



EXPERIMENTAL

***cis*-3-Hexenyl-*p*-toluenesulfonate (II).** To an ice-cold, stirred solution of 1.00 kg (10.0 moles) of *cis*-3-hexen-1-ol (Research Organic Chemicals, 95% *cis* : 5% *trans* by gas-liquid chromatography analysis) in 3.25 liters of pyridine was added 2.11 kg (11.0 moles) of *p*-toluenesulfonyl chloride over 4 hr. The mixture was refrigerated for two days, diluted with 6 liters of water and extracted with six 900-ml portions

of dichloromethane. The combined organic extracts were washed with 6 liters of water, 2 liters of 12*N* sulfuric acid (final pH 2-3), and dried over anhydrous potassium carbonate. The solvent was removed in vacuo to leave 2.19 kg (86%) of the syrupy tosylate ester; $\lambda_{\text{film}}^{\text{max}}$ no OH, 8.6 μ ($-\text{SO}_2\text{OR}$).

***cis*-6-Nonen-2-one (III).** To a stirred solution of sodium ethoxide in 4.33 liters of ethanol (from 159 grams, 6.9 g-atoms of sodium) was slowly added 876 ml (6.9 moles) of ethyl acetoacetate. The warm mixture was stirred for 1 hr, then 1.46 kg (5.7 moles) of tosylate (II) was added. Heat was applied for about 15 min and removed as the reaction became exothermic, with precipitation of sodium tosylate. After 1 hr, heating was resumed to maintain a gentle reflux for another hour. The mixture was cooled, neutralized (pH 7-8) with glacial acetic acid, and was distilled of about 3.5 liters of alcohol. The residue was diluted with 2 liters of ice water and the upper organic layer separated. The aqueous portion was extracted twice with 500-ml portions of dichloromethane. The combined organic extract was washed with 2 liters of water, dried over magnesium sulfate, and the solvent evaporated to leave 1.21 kg (99%) of syrupy keto ester intermediate.

A mixture of this syrup, 343 grams (8.6 moles) of sodium hydroxide, and 5.73 liters of water was stirred at room temperature for 48 hr. After an ether wash (500 ml) the aqueous portion was acidified (pH 2) with 18*N* sulfuric acid and heated at 90°C for 5 hr, effecting smooth decarboxylation. The organic layer was separated and the aqueous layer extracted twice with 500-ml portions of ether. The total organic extracts from three identical runs were combined, washed with 5% sodium bicarbonate solution, and dried over magnesium sulfate. After removal of the ether by distillation through a Vigreux head, the product was collected at bp 102-103°C (50 mm) to yield 889 grams (37%), 95% pure *cis*-6-nonen-2-one by gas-liquid chromatography.

Semicarbazone, mp 88-90°C, recrystallized from cyclohexane. Anal. Calcd. for $\text{C}_{10}\text{H}_{18}\text{N}_2\text{O}$: C, 60.9; H, 9.71; N, 21.3. Found: C, 61.1; H, 9.89; N, 21.4.

***exo*-Brevicomins (V).** To a stirred, cold (5°C) solution of 279 grams (2.0 moles) of the *cis*-6-nonen-2-one in 4.2 liters of benzene was added 403 grams (2.0 moles) of 85% *m*-chloroperbenzoic acid over 40 min; the temperature was kept below 15°C. The mixture was allowed to warm to room temperature and then was heated to boiling for over 2 hr. After a 4-hr reflux the mixture was cooled to 10°C, filtered, and the white solid residue washed with cold benzene. The filtrate was washed successively with 1 liter of saturated sodium bicarbonate solution, 500 ml of 5% sodium bisulfite, and 1 liter of bicarbonate. After combination with 2 similar runs, the total extract was dried over magnesium sulfate and most of the benzene removed by distillation through a Vigreux head. The residual solution was distilled through a spinning band column to give 550

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